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(54) Title: CHEMICAL COMPOSITION FOR TREATING CERVICAL INTRAEPITHELIAL NEOPLASIA I, II, III, IV AND CERVICITIS

(57) Abstract

The present clinical studies with tea catechin as a major chemical component demonstrated that tea catechin when applied to human papilloma virus associated with cervical intraepithelial neoplasia I, II, III, and IV including chronic cervicitis are either preventable from further progression of disease state and/or cured completely following topical application and/or oral medication to cervical area without any serious side effects. Patients can easily apply topically or insert as a suppository insert, or oral medication of tea catechin capsules by patients, themselves.

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CHEMICAL COMPOSITION FOR TREATING CERVICAL INTRAEPITHELIAL NEOPLASIA I, II, III, IV AND CERVICITIS

TECHNICAL FIELD

The present invention relates to the new use of tea catechin as a major chemical component to prevent or to treat cervical intraepithelial neoplasia I, II, III, and IV including chronic cervical cervicitis caused by human papilloma virus or more specifically to a chemical composition for preventing or treating cervical intraepithelial neoplasia or cervicitis.

BACKGROUND ART

Cervical cancer is the second most common malignancy in women worldwide and remains a significant health problem for women. Overall survival remains 40% and new strategies, based on the clinical and molecular aspects of cervical carcinogenesis, are desperately needed. Cervical carcinoma is frequently associated with human papilloma virus (HPV) types 16 and 18 infection, that often immortalize human cervical epithelial cells. This immortalization is due to two early gene products, the E6 and E7 proteins, and overexpresion of these two proteins is essential step in carcinogenesis. The most common types of HPV are those classified as high risk (HPV 16, 18, 45, and 56), intermediate risk (HPV 31, 33, 35, 51, 52, and 58). These HPV subtypes are associated with CIN I, II, III, and IV cervical intra- and/or interepithelial neoplasia, while the HPV subtypes 6 and 11 are only associated with condyloma acuminata, a common genital warts. The high and intermediate risk types have been identified in 77% of high grade cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesion (SIL) and in

84% of invasive lesions. Cohort studies demonstrated that women with HPV infection have 11-60 times increased risk of developing high grade CIN and 15-50 times increased risk of developing invasive cancer than do women without HPV infection. Despite the fact that the cervix is easily accessible, that a relatively good screening test exists and has been in use for decades, and that new therapeutic initiatives using surgery, radiotherapy, and chemotherapy have been tried, survival remains dismal 40% worldwide. Therefore, novel strategies to prevent or delay CIN I, II, III, and IV to invasive cervical carcinoma are desperately needed. Modes of treatment for cervical intraepithelial neoplasia have been LEEPconization, and/or surgical removal, but there are no effective drug therapy and thus desperately in need to develop chemopreventive therapy for CIN I, II, III, and IV and to prevent invasive progression of CIN I, II, III, and IV intraepithelial neoplasia to malignant cervical carinoma.

DISCLOSURE OF THE INVENTION

Therefore, the treatment of cervical intraepithelial neoplasia caused by HPV is highly desired. Catechin ointment, suppository or capsule for oral medication are very easy to administered by patients and the clinical results of both topical application and topical application in combination with oral intake of tea catechin capsules resulted in excellent clinical results within 8-12 weeks of treatment with high degree of safety and high degree of convenience in their use.

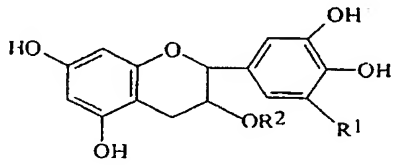
We, the present inventors clinically tested tea catechin as a preventive and/or a therapeutic agent for patients diagnosed as CIN I, II, III, and IV or cervical cervicitis by colposcopy, and cytology examination, and quantitation of HPV DNA content. These cohorts were subjected to either topical application directly to cervical area, and/or in combination of oral tea catechin capsules. Duration of the treatment was 6-12 weeks of

topical application and if the therapeutic response was weak, then those patients were given oral dose of tea catechin b.i.d while continuing topical application of tea catechin ointment twice a week. The clinical studies showed that majority of patients responded completely to either topical and/or in combination with oral treatment. No notable serious side effects were observed.

Thus the present invention relates to a composition for a treatment of cervical intraepithelial neoplasia caused by human papilloma virus containing tea catechin as a main component.

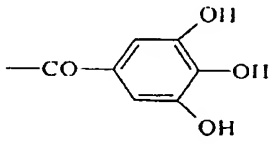
BEST MODES FOR CARRYING OUT THE INVENTION

The tea catechin of the present invention is shown below in the general formula I.



(I)

Wherein R^1 represents H or OH and R^2 represents H or



The tea catechins (e.g. *Camellia sinensis*) are more specifically, epicatechin, epicatechin gallate, epigallocatechin gallate, gallocatechin etc. (including derivatives thereof). These catechins can be used singly or two more may be mixed together. Out of these, it is particularly desirable to have (-)-epigallocatechin gallate as a main component.

Epigallocatechin gallate is a major component that should be in combination with any other tea components listed above in an appropriate proportions. For example: Polyphenon^{ETM} (Mitsui Norin Co.; Composition: (-)-epigallocatechin gallate 54.8%, (-)-epicatechin 14.7%, (-)-epicatechingallate6.7%, (-)-epigallocatechin 6.0%, (-)-gallocatechin gallate 4.0%).

The prevention and/or treatment for cervical intraepithelial neoplasia stage I, II, III, and IV including cervical cervicitis of the present invention could be used for example in the form of ointment such as cream, jelly, emulsion; or in the form of suppository such as a capsule, and usually the tea catechin component is combined with an excipient, extending agent, emulsifier, dispersing agent, etc. Vaseline is suitable as a base for the ointment. For the ointment the content of tea catechin should be between 5-20% by weight, preferably between 12-18% by weight, more preferably 15% by weight. In the case of suppository the content of tea catechin should be 100-500 mg/catechin, preferably 200-300 mg/capsule, or more preferably 200 mg/capsule.

A typical usage example for the ointment is to apply directly to the cervical lesion, vaseline cream containing 5-20% weight catechin from twice per week for a period of 4-12 weeks or more. Or a typical usage example the cervical intraepithelial neoplasia I, II, III, and IV or cervicitis is to insert a suppository containing 100-500 mg tea catechin, from twice per week for period of 4-12 weeks or more. If the CIN I, II, III, and IV is persistent to topical treatment, then daily 200 mg Poly^{ETM} capsule/b.i.d. in combination with topical application 2 times a week is continued for up to 8 weeks or more.

There is no danger of side-effects from the treatment for cervical carcinoma in situ I, II, III, and IV stages with the composition of the present invention having tea catechin as the main component thereof since the main component is a natural substance derived from tea which is commonly consumed regularly, and it may be taken for long periods of time. Moreover this medication may be easily applied to or inserted in the infected area

by the patients themselves. The composition of the present invention for prevention and/or a treatment of cervical carcinoma in situ I, II, III, and IV or cervicitis is tea catechins, which is natural substance derived from tea, which is commonly consumed regularly and it may be taken for long periods of time. Moreover this medication may be easily applied to, inserted into cervical area via vagina easily, and or/in combination with a tea catechin capsule orally by patients themselves. The composition of the present invention for a prevention and/or treatment of CIN I, II, III, and IV or cervical cervicitis has a very high potential for prevention and/or treatment to prevent and/or treat CIN I, II, III, and IV (including cervicitis) so as to prevent further development to malignant cervical carcinoma. Another aspect of the invention is a method of application in combination of oral treatment and dosage(s) of tea catechin that is effective against human papilloma infected cervical intraepithelial neoplasia I, II, III, and IV or cervical cervicitis. Human papilloma virus infection level in cervical epithelium is completely eradicated or significantly reduced by tea catechin containing (-)-epigallocatechin gallate as a major component.

EXAMPLES

The present invention will be explained in more detail with reference to the following examples which are in no way meant to limit the scope of the invention.

Test Example 1

Clinical tests of the present invention were carried out at the Department of Obstetrics & Gynecology, Kang Nam St. Mary's Hospital, Catholic University Medical Center, Catholic Medical College, Seoul, Korea. The total of 22 patients diagnosed as

CIN I, II, III, and IV including cervical cervicitis were treated topically 2 times a week with tea catechin ointment (Poly E) for the duration of 6-12 weeks. Patients who failed to respond to topical ointment was given polyphenon E capsule (200 mg/capsule) 2 times a day (400 mg/day), while topical treatment continued. Following 6-10 weeks of topical treatment, the clinical results showed 16 complete responders (out of 22 patients), 3 partial responders, and 3 non-responders (Table 1). In the cervicitis patient group, 7 out of 8 showed complete response to topical treatment, while one patient was not responsive (90% response rate). In the CIN I patient group, 6 out of 8 showed complete response, 1 showed a partial response, and 1 did not respond and this patient was subjected to LEEPConization (approximately 80% response rate). Two CIN II patients responded completely to topical treatment (100% response rate). In CIN III and IV patient group, topical treatment showed 1 complete response, 2 partial response and 1 no response (75% response rate). Complete responses means a complete cure.

In contrast, 7 patients consisted of 2 cervicitis, 3 CIN II, and 2 CIN III were treated with a combination of both topical and oral treatment for 8-12 weeks. The clinical results showed that all patients responded completely with an exception of one CIN II patient did not return for clinical evaluation (85-100% response rate)(see Table 2).

Table 1

Chemoprevention Clinical Study Data (Poly E)

Tropical Application

No.	Patient No.	Patient's Name	Age	Patho-logy	HPV DNA Before Treatment	HPV DNA After Treatment	Treatment Schedule No. Week^{-1}	Duration (Week)	Side Effects	Thera-peutic Results
1	25-7	J. O. Kim	34	CC	-	(-)	2	8	-	Complete Response
2	31	S. H. Y	39	CC	18.7	-	2	8	-	Complete Response
3	32	Y. J. Y	29	CC	1.95	-	2	8	-	Complete Response
4	30	M. O. C	28	CC	57.9	51.3	2	8	-	Persistent
5	2-1	Y. M. Choi	29	CIN I	43.21	1.23	2	8	-	Complete Response
6	3-1	Y. K. Chung	34	CIN I	17.0	1.23	2	11	Itching Slight fever for the 1st day of treatment	Complete Response
7	10-4	M. B. Kim	30	CIN I	31.1	4.28	2	6	-	Complete Response
8	8	Y. S. L	38	CIN I	38.9	-	2	8	-	Complete Response
9	11	O. H. K	38	CIN I	-	-	2	8	-	Complete Response
10	18	H. J. P	27	CIN I	2.8	-	2	8	-	Complete Response
11	29	H. J. Y		CIN I	7.1	-	2	8	-	Complete Response

Table 2

Chemoprevention Clinical Study Data (Poly E)

Oral Administration

No.	Patient No.	Patient's Name	Age	Patho-logy	HPV DNA Before Treatment	HPV DNA After Treatment	Treatment Schedule No. Week[-1]	Duration (Week)	Side Effects	Therapeutic Results
12	8	Y. S. Lee	38	CIN I	38.9	4.23	2	6	-	Partial Response
13	23-6	Y. S. Yim	33	CIN I	2.8	(-)	2	8	-	Partial Response
14	7-3	S. R. Lee	29	CIN II	3.1	(-)	2	8	-	Complete Response
15	26	Y. J. C	45	CIN II	13.1	-	2 2+ poly E 200mg	8	-	Complete Response
16	28	S. O. C	38	CIN II	9.2	-	2	8	-	Complete Response
17	26	J. H. Chang	45	CIN II	13.1	(-)	2 2+ poly E 200mg	8	-	Partial Response
18	15-5	C. N. Kim	43	CIN III	1.97	(-)	2	6	-	Complete Response
19	19	M. Y. Sung	34	CIN III	1.28	(-)	2 2+ poly E 200mg	12	-	Complete Response
20	27	H. K. Choi	40	CIN III	23.3	(-)	2	10	-	Partial Response
21	24	M. O. Y	35	CIN III	13.3	23.6	2 2+ poly E 200mg	8	-	Persistent
22	21	J. O. L	43	CIN IV	4.3	-	2	8	-	Partial Response

Test Example 2

Clinical tests were carried out at the Department of Obstetrics & Gynecology, Kang Nam St. May's Hospital, Catholic University Medical Center, Catholic Medical College, Seoul, Korea. The total of 41 patients diagnosed as CIN I, II and III including cervical cervicitis were treated topically 2 times a week with Polyphenon E ointment for

the duration of 8 weeks. Among these 41 subjects, 33 were treated with only topical application of Polyphenon E ointment, while the remaining 8 were given Polyphenon E capsule (100mg catechin/capsule) two times a day for 8 weeks in addition to the topical application. All patients completed the requirements of pretreatment evaluation and consented to cytology, cervicography, colposcopy, HPV DNA analysis, and cervical biopsy for histoligic evaluation. Evaluation criteria were colposcopy, cervicography, cytology, histology, nuclear morphometry, and HPV DNA analysis by PCR technology.

Results in Table 3 show much higher responding rate by the combination therapy i.e. topical application and oral intake in combination than topical application alone.

Table 3

	No. of Patients	Responder	Non-responder
P-E Ointment	33	19 (58%)	14 (42%)
P-E Ointment plus P-E Capsule	8	6 (75%)	2 (25%)

INDUSTRIAL APPLICABILITY

From these clinical results, it is clear that a combination therapy is superior to that of topical treatment alone, especially for the advanced stage of cervical intraepithelial neoplasia (e.g. CIN III or IV or non-responders). Clinically, we have demonstrated that either topical, suppository, and/or capsules for oral administration of tea catechin can prevent, cure or partially cure cervical cervicitis, cervical intraepithelial neoplasia stages

I, II, III, and IV. Thus, tea catechin can be used as either chemopreventive and/or as a therapeutic agent to cure and also to prevent or delay malignant development to cervical carcinoma.

CLAIMS

1. A chemical composition for preventing and/or treating cervicitis, cervical intraepithelial neoplasia (CIN I, II, III, and IV) associated with human papilloma virus (HPV subtype 16, 18, 45, 56, 31, 33, 35, 51, 52 and 58) in women, which comprises a tea catechin as a major chemical component in an amount and frequency of dosing most effective for treating cervicitis, cervical intraepithelial neoplasia.

2. A method of preventing and/or treating cervicitis, cervical intraepithelial neoplasia (CIN I, II, III, and IV) associated with human papilloma virus (HPV subtype 16, 18, 45, 56, 31, 33, 35, 51, 52 and 58) in women, with the chemical composition of claim 1 which is in the form of an ointment or a suppository, or a capsule for oral use.

3. The method according to claim 2, wherein said composition is in the form of an ointment having 5-20% by weight of tea catechin and in the form of a suppository or a capsule for oral use each contain 100-500mg of the tea catechin, respectively.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR99/00651

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K31/353, 9/02, 9/06, 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0842660 A1 (CANCER INSTITUTE (HOSPITAL) CHINESE ACADAMY OF MEDICAL SCIENCES) 20 May 1998 (20.05.1998) totality.	1-3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
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Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A1	842660	20-05-1998	AU	A1	44438/97	04-06-1998
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